Antihyperalgesic Effect of the N-methyl-D-aspartate Receptor Antagonist Dextromethorphan in the Oral Surgery Model

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Peripheral neuronal barrage from tissue injury produces central nervous system hyperexcitability through the activation of N-methyl-D-aspartate (NMDA) receptor sites by excitatory amino acids and neuropeptides. This study evaluated if attenuation of NMDA receptor activation with dextromethorphan (DM) suppresses the postoperative development of hyperalgesia. Seventy-five patients undergoing oral surgery in a parallel-group, double-blind study randomly received either a placebo or the maximally tolerated dose of DM administered orally prior to and continuing for 48 hours following surgery. Pain as measured by category, visual analog, and verbal descriptor scales was not significantly different between groups during the first 6 hours following surgery. However, pain at 48 hours was decreased in the DM group as measured by scales for pain intensity and unpleasantness. Subjects in the DM group also self-administered fewer acetaminophen tablets for unrelieved pain over 24 to 48 hours postoperatively. The results suggest that DM at maximally tolerated doses does not produce an analgesic effect in the immediate postoperative period but reduces pain at 48 hours. This may be related to antagonism of NMDA receptors necessary for the expression of hyperalgesia associated with noxious afferent input postoperatively.

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INTRODUCTION

A growing body of data suggests that both acute and chronic pain states involve processes of central hyperexcitability that may be mediated, in part, by the action of excitatory amino acids at N-methyl-D-aspartate (NMDA) receptors.[1-3] Autoradiographic data confirm the presence of a significant number of NMDA binding sites in the rat spinal dorsal horn.[4] NMDA produces excitatory responses in spinal dorsal horn nociceptive neurons of rats and primates, as measured by a variety of in vitro and in vivo electrophysiologic techniques.[5-9] Nociceptive transmission within the rat dorsal horn is partly mediated through NMDA receptors.[9-12] NMDA receptors in the rat are also involved in the phenomenon of "windup,"[13] a state of central sensitization mediated by C-fiber input,[14,15] and in the induction and maintenance of central sensitization produced by C-fiber afferent input.[16]

Blockade of NMDA receptors in rats attenuates the magnitude and duration of thermal hyperalgesia induced by intradermal injection of complete Freund's adjuvant and carrageenan.[17] The increased receptive field size of nociceptive neurons accompanying this hyperalgesia is reduced by the NMDA receptor antagonist MK-801, supporting the role of NMDA receptors in the dorsal horn plasticity and behavioral hyperalgesia that follows peripheral tissue inflammation. NMDA antagonists also reduce mechanical hypersensitivity in rats, primates, and cats under a wide variety of circumstances[7,18-23] as well as formalin-induced nociceptive behavior.[24] Dextromethorphan (DM) selectively reduces the temporal summation of second pain in humans, a phenomenon that is thought to reflect some

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of the mechanisms underlying centrally mediated hyperalgesia.[25] Administration of the NMDA receptor blockers MK-801 and 5-APV just prior to neurectomy in rats significantly suppresses autotomy,[26] a process thought to be analogous to neuropathic pain in humans, further suggesting NMDA receptor modulation of central sensitization following nerve injury. These data and many other similar observations form the basis for evaluating the role of NMDA receptors in pain and the analgesic effects of putative NMDA receptor blockers clinically.

Two drugs used clinically for indications other than pain, ketamine and dextromethorphan, have been demonstrated to act as NMDA receptor antagonists.[27] Ketamine is an intravenous anesthesia induction agent that relieves pain due to postherpetic neuralgia,[28] chronic posttraumatic pain and allodynia,[29,30] pain due to central nervous system (CNS) injury,[31] and acute postsurgical pain.[32,33] The parenteral route of ketamine administration and its side effect profile, which is attributed to high-affinity binding at the NMDA receptor,[34] limits use in ambulatory patients. Low-affinity NMDA receptor antagonists are hypothesized to have greater therapeutic potential due to lower toxicity than high-affinity antagonists by permitting a higher ratio of normal ongoing activity at NMDA receptors.[34]

DM is a low-affinity NMDA receptor blocker that is rapidly metabolized to dextrorphan, which also acts as an NMDA antagonist.[27] DM is widely used as a nonopioid cough suppressant and is well tolerated at antitussive doses (120 mg/day). DM has been shown to reduce pain behavior in animal models[22,29] and in a clinical trial of painful diabetic neuropathy, but not postherpetic neuralgia.[35] McQuay et al, however, reported that oral dextromethorphan did not reduce pain from a variety of peripheral and CNS lesions in a group of 19 patients.[36] It is unclear from these data if DM produces analgesia acutely or attenuates more slowly occurring hyperalgesia or if it is tolerated at the high doses often needed to demonstrate activity.

Oral surgery has become a standard model for predicting the clinical efficacy of investigational analgesics and evaluating mechanisms of pain and analge sia.[37-39] The activation of oral structures by tissue-damaging stimulation results in a neural barrage in the trigeminal brain stem nucleus, mainly at its most caudal level—the subnucleus caudalis, also referred to as the medullary dorsal horn.[40] The latter name was adopted because of its similarity with the spinal dorsal horn, the termination site of nociceptive neurons whose receptors are located at the level of spinal dermatomes. The oral surgery model has been demonstrated to be sensitive for detecting the clinical effects of central hyperexcitability manifesting as increased pain over the first 2 postoperative days.[41,42] This study used the oral surgery model in a randomized, double-blind, placebo-controlled clinical trial to evaluate the hypothesis that NMDA receptor blockade with DM can suppress the development of postoperative hyperalgesia. The results suggest that DM at maximally tolerated doses does not produce an acute analgesic effect in the immediate postoperative period but attenuates pain at later time points associated with the development of central hyperexcitability.

METHODS

The sample consisted of 75 healthy oral surgery outpatients referred to the National Institutes of Health Pain Research Clinic for the surgical removal of impacted third molars. Inclusion criteria included two to four partial or full bony impacted third molars with exclusion for the concurrent use of analgesics, antihistamines, antidepressants, and CNS depressants; history of allergy to DM; and pregnancy or lactation. Subjects were informed of the risks from oral surgery and DM and signed an institutionally approved consent form. The clinical protocol was approved by the National Institute of Dental Research Institutional Review Board.

Drug (30 mg per capsule) and matching placebo were formulated, randomized, and allocated by the NIH Pharmaceutical Development Service. On the day prior to surgery, subjects were instructed to self-administer two capsules of drug or placebo at dinner time and, if tolerated, to administer two additional capsules before going to bed. On the day of surgery, subjects were questioned regarding the incidence of any adverse effects—usually drowsiness or dizziness—and administered two to four capsules 1 hour prior to surgery, based on the dose tolerated the evening before surgery. Patients were sedated immediately prior to surgery with 3 to 5 mg midazolam administered intravenously followed by intraoral local anesthetic injections of lidocaine with epinephrine (1:100,000). This resulted in patients who were conscious during the procedure but did not respond to surgical stimulation due to the local anesthetic.

Subjects remained at the clinic after surgery for 6 hours for observation of pain response and the incidence of adverse reactions. Pain medication (acetaminophen) was administered if requested for the relief

of moderate pain. For severe pain unrelieved by the acetaminophen, ketorolac 30 mg was administered intravenously. Dextromethorphan or a matching placebo was given at discharge with instructions to take two to four tablets every 6 hours as directed based on the dose tolerated on the evening before surgery and their response to the dose given at the clinic on the morning of surgery. Acetaminophen (975 mg) was also provided, to be taken only as needed for pain unrelieved by the study drug.

Adverse effects, analgesic intake, and pain as assessed by a 4-point category scale, 100 mm visual analog scale (VAS), and verbal descriptor analog scales for pain intensity and unpleasantness[43] were recorded hourly on the day of surgery and upon awakening prior to ingestion of medication at 24 and 48 hours. Subjects returned to the clinic at 24 and 48 hours postoperatively to evaluate compliance and to modify the dosing regimen, if necessary, based on their response to the administered dose. Subjects were maintained at the maximum number of capsules (DM or placebo) based on their self-reported adverse effects, such that the maximally tolerated dose was achieved over the 48-hour observation period.

Data were analyzed with the BMDP Statistical Software Package (SPSS, Inc., Chicago, IL). Pain intensity over the 6-hour postoperative observation period was evaluated by repeated measures analysis of variance as a measure of any analgesic effect in the immediate postoperative period. Pain at 24 and 48 hours was treated as an independent measure of central hyperalgesia based on previous clinical trials in the oral surgery model demonstrating antihyperalgesic effects that could only be distinguished at 48 hours.[41,42] Statistical differences between the two groups at 24 and 48 hours were determined by the student's *t*-test for continuous variables (VAS, verbal descriptor analog scales) and the Mann-Whitney test for categorical data. The number of acetaminophen tablets ingested per 24-hour period and the incidence of side effects were compared between the two groups by chi-square analysis. For all statistical tests, p-values < 0.05 in a two-tailed test were considered significant. A sample size of 30 subjects per group was calculated based on a previous study using the oral surgery model[44] to detect a 30% reduction in pain by DM in comparison to the placebo with a power of 0.80.

RESULTS

The demographic characteristics of the sample were similar between the drug and placebo groups for age, sex, height, and weight (Table I). Intraoperative variables such as anesthetic dosages and surgical difficulty were also similar between groups. Similarities between these variables suggest that differences between groups were not due to variations in surgical procedure or anesthetic agents used.

Table I Demographic Characteristics and Intraoperative Variables

	Placebo	Dextromethorphan
Sex (*n*)		
M	25	24
F	14	12
Age (years)	21.5 ± 0.6	22.0 ± 0.8
Height (cm)	166.5 ± 4.9	170.1 ± 3.2
Weight (kg)	77.9 ± 3.8	72.9 ± 3.2
Midazolam (mg)	3.2 ± 0.1	3.0 ± 0.1
Lidocaine (mg)	200.3 ± 5.7	195.5 ± 4.8
Surgical difficulty*	9.2 ± 0.3	9.8 ± 0.3

* Sum of difficulty scores per extraction site, where 1 = *simple*, 2 = *soft tissue*, 3 = *partial bony*, 4 = *full bony impaction*. Values are mean ± *SD*.

Pain was similar between groups during the immediate postoperative period, as measured by all scales (Table II) and illustrated for the VAS (Figure 1), with all subjects requesting analgesics as the local anesthetic dissipated. There were no significant differences between groups in the receipt of rescue analgesics during this time period, although six patients in the placebo group and two in the DM group required administration of injectable ketorolac for pain unrelieved by the initial dose of acetaminophen (975 mg).

By 24 hours, there was a trend for the drug group to report less pain than the placebo group (Figure 2, upper panel); there was no difference in the amount of self-administered rescue analgesic consumed (Figure 2, lower panel). Pain at 48 hours was significantly lower in the DM group, as measured by all pain scales (Table II) and illustrated for the VAS (Figure 2, upper panel). In addition, subjects in the DM group self-administered significantly ($p < 0.05$) fewer acetaminophen tablets for unrelieved pain during the 24- to 48-hour period (Figure 2, lower panel). The number of study drug capsules consumed ranged from 2 to 16 per day (60-480 mg per day). The mean DM dose was 336 ± 101 mg during first 24 hours following surgery, and a mean of 309 ± 104 mg was consumed from 24 to 48 hours postoperatively.

Incidence of adverse effects was slightly elevated in the DM group during the immediate postoperative period. However, over the 6- to 24-hour and second 24- to 48-hour periods, the DM group experienced

Table II Pain as Measured by Scales Other Than the Visual Analog Scale

	Time Postsurgery (hours)										
	1	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**5**	**6**	**24**	**48**
Category scale											
Placebo	0.4	0.9	1.3	1.8	2.1	2.2	2.3	2.2	2.2	1.4	1.4
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1
Dextromethorphan (DM)	0.5	0.9	1.4	1.9	2.1	2.3	2.3	2.3	2.3	1.3	0.9*
	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1	± 0.1
Pain intensity											
Placebo	28.3	44.6	67.8	96.6	117.9	126.0	127.4	127.1	127.2	75.3	76.1
	± 7.1	± 7.1	± 7.5	± 7.9	± 6.4	± 6.0	± 5.7	± 5.9	± 5.9	± 7.6	± 8.4
DM	41.1	57.7	85.7	109.3	119.9	126.0	126.1	126.7	126.1	71.4	52.5*
	± 7.1	± 7.5	± 7.1	± 6.6	± 5.2	± 4.8	± 4.9	± 4.8	± 4.9	± 6.9	± 6.5
Unpleasantness											
Placebo	44.1	50.5	65.0	87.5	103.9	111.6	112.9	112.5	112.6	72.3	66.8
	± 6.1	± 5.9	± 5.9	± 6.5	± 6.4	± 5.8	± 5.6	± 5.7	± 5.7	± 5.2	± 7.3
DM	45.0	51.2	70.0	90.5	101.4	106.7	107.0	107.4	106.5	68.9	57.6*
	± 5.1	± 5.7	± 5.3	± 5.5	± 4.8	± 4.4	± 4.5	± 4.4	± 4.6	± 5.0	± 5.2

*$p < 0.05$ versus placebo.

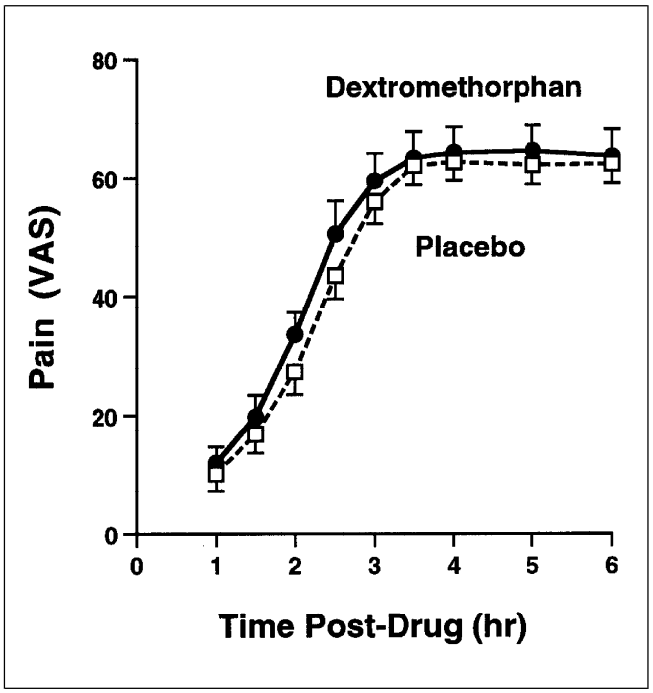

Figure 1. Pain over the first 6 hours postoperatively as measured by the visual analog scale.

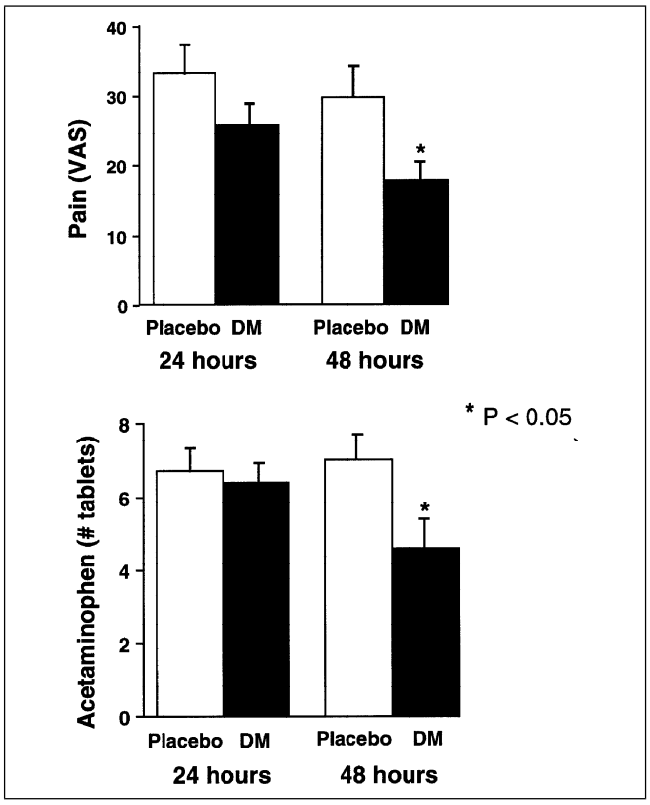

*Figure 2. Pain at 24 and 48 hours postoperatively as measured by visual analog scale (upper panel, *p = 0.02) and number of acetaminophen tablets self-administered for unrelieved pain (lower panel, *p = 0.03).*

significantly more adverse effects (Figure 3). The most frequently reported side effects were dizziness, drowsiness, headache, and blurred vision. Four subjects were discontinued from the study due to intolerable adverse effects on the day of surgery. Of these, two were secondary to allergic reaction, one to ataxia, and one due to prolonged lip paresthesia.

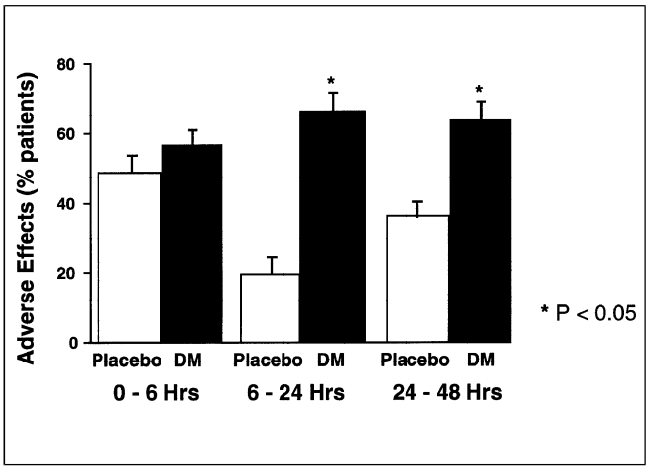

Figure 3. Incidence of adverse effects in the initial 6 hours and over the subsequent 6- to 24-hour and 24- to 48-hour periods.

DISCUSSION

DM at maximally tolerated doses reduced postoperative pain 2 days following oral surgery without demonstrating an acute analgesic effect immediately following surgery or at 24 hours. These findings agree with previous clinical studies demonstrating that NMDA receptor antagonists differ from traditional analgesics in their mechanism of action.[45] They have no effect on the initial nociceptive input, as seen over the first 6 hours postoperatively, but reduce injury-induced facilitation of CNS mechanisms at later time points—48 hours following surgery in this study. Drugs of this class should exert an analgesic effect only under conditions in which tissue injury (e.g., burn injury) or repetitive nociceptive stimulation (e.g., during inflammation) has induced central hyperexcitability.

In contrast to animal experiments, previous clinical studies have not shown consistent agreement concerning the efficacy of DM for either experimental or chronic pain states. For example, Price et al[25]

demonstrated that DM reduces temporal summation of second pain, yet the same range of doses was ineffective for experimental ischemic and capsaicin pain.[46] In clinical trials, DM was effective for diabetic neuropathy,[35] but others have failed to demonstrate an effect for similar neuropathic pain states[36] and postherpetic neuralgia.[35]

Methodologic differences may explain these equivocal findings from clinical studies in chronic conditions: the concurrent use of analgesics other than DM in some studies, differences in baseline pain ratings within and across studies, the type of pain condition treated, and differences in dosing regimens may all have contributed to differences in findings across clinical trials. In this study, subjects were healthy volunteers, experiencing acute postoperative pain that is primarily inflammatory in origin (for a review, see Dionne[39]) and sensitive to the effects of anti-inflammatory drugs such as aspirin and the NSAID class.[37] The lack of effect during the immediate postoperative period may reflect limited potency of the analgesic manipulation when pain is at its highest, while the demonstration of reduced pain and decreased use of a rescue drug in the DM group at later time points may represent a DM-mediated attenuation of hyperalgesia.

The adverse effects observed in this study were not unexpected, considering the well-documented side effect profile of DM.[47] The incidence was high in comparison to previous studies, most likely because of the accelerated increase in dose in this study over the course of 3 days when compared to chronic pain trials in which the drug is titrated to effect over several weeks. Although poor metabolizers of DM were not characterized, it is also possible that slow elimination of DM in the face of a rapidly increasing dose may have contributed to the observed incidence of adverse effects in some subjects.

Comparison of analgesic intake between groups is a traditional outcome measure in studies evaluating postoperative pain. Subjects in the placebo group tended to self-administer more acetaminophen for unrelieved pain within the first 24 hours (nonsignificant) and over the 24- to 48-hour period ($p < 0.05$). This greater analgesic intake by the placebo group likely minimized group differences in the pain report. Any prolonged anti-inflammatory effect of the ketorolac administered as a rescue analgesic on the day of surgery could have also minimized differences between groups. These factors may account for our inability to detect a difference between groups at 24 hours.

These data support the hypothesis that NMDA receptor antagonists suppress the development of central sensitization, which contributes to increased postoperative pain. Moreover, they provide further evidence that nociceptor afferent barrage permits the development of changes within the CNS that manifest as increasing pain, often characterized as central hyperexcitability. Although the lack of effect in the immediate postoperative period and the elevated incidence of adverse effects at these doses do not support the use of DM alone as a postoperative analgesic, these observations suggest that NMDA receptor antagonists such as DM may be useful pharmacologic interventions to reduce hyperalgesia or mitigate chronic pain. If the clinical potential of DM as a pain therapy is to be further explored, it should be evaluated at lower doses and in combination with other analgesics. An alternative strategy would be to develop agents with specificity for peripheral NMDA receptors that might mediate analgesia peripherally without the high incidence of side effects presumably due to the central effects of DM.

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